REMARKS

Claims 1-4, 6-20, and 24-28 were examined and rejected. The Examiner objected to claims 24 and 26 (and indicated them to be patentable if written in independent form or if they depended from a patentable parent claim).

First, Applicants thank Examiner Fronda and SPE Nashed for the courtesy of a personal interview conducted on October 21, 2008, in which the pending claims, proposed amendments, support of the claims under § 112, first paragraph (enablement and written description), and the unobviousness of the claims was discussed.. The substance of the interview is discussed in more detail below. The interview summary provides a rather broad statement, acknowledging that all the pending claims were discussed though it lacks any specific detail about what was discussed (noting only two references of the several that were provided in advance and discussed). The Summary indicates the Office's non-committal position as to whether Applicants' proposed amendments and arguments would suffice in overcoming the rejections. In this interview, a number of references supporting Applicants' proposed amendments and the enablement of the proposed claims were discussed (including the two noted in the Summary Record, Meaden *et al.* and Bhosale *et al.*). These and several other references are discussed in more detail in the Van Dijken Declaration and in Applicants' remarks below.

Applicants thank the examiner in advance for the offer (noted in the interview summary record) to discuss the Office's reaction to the present amendments and arguments, for example, before the final issuance of the next Action.

To place the claims in a more logical order, which had been "lost" during the prosecution history of this case, Applicants have chosen to replace the prior claims with newly numbered claims that include amendments to be discussed below. Table 1 below shows the correspondence between the prior claims and the new claims.

Table 1

New claim	Based on prior claim(s):	Claims Rej § 103
29	12	
30	12, 2	
31	13	
32	14	
33	15	
34	16	
35	16	
36	16	
37	17	
38	20, 11	
39	1	**103**[1]
40 [3]	24 [2]	
41	2	**103**[1]
42	18	
43	3	**103**[1]
44	4	**103**[1]
45	19	
46	6	
47	7	
48 [3]	26 [2]	
49	8	
50	9	
51	10, 1	
52	10	
53	10	
54	4	
55	10	
56	11	

[1] "103" indicates that prior claim (1, 2, 3 and 4) was rejected as obvious.

[2] claims that would have been allowable - if not dependent on rejected base claim

[3] claims that depend from "new" claim 39, which is an amended form of prior claim 1, believed to be allowable as dependent from an allowable base claim.

I. Rejections under 35 U.S.C. §112, 1st Paragraph (Written Description)

Claims 1-4, 6-20, 25, 27, and 28 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description** requirement.

According to the Office, the claims encompass a genus of nucleic acids comprising a nucleotide sequence encoding xylose isomerase ("XI") having an amino acid sequence which is 95% identical to SEQ ID NO: 1. The scope of this genus is said to include many members with widely differing nucleotide and/or amino acid sequences and structures. The genus is highly variable because a significant number of structural and biological differences exist between genus members. The claimed nucleic acid comprising a nucleotide sequence encoding XI represents a partial structure. The specification does not teach which amino acid residues can be altered (by substitutions, deletions, additions, insertions, and combinations thereof) or modified while maintaining catalytic activity. One of ordinary skill in the art would therefore be unable to

identify which particular residues in SEQ ID NO: 1 can be altered while maintaining XI activity without further testing.

The specification discloses the polynucleotide SEQ ID NO: 2 encoding a polypeptide SEQ ID NO: 1 with XI activity but does not describe and define any structural features, nucleotide and/or amino acid sequences, and/or biological functions that are commonly possessed by members of the genus. The specification dos not provide a correlation between any structure, other than the indicated sequences, and XI activity which would allow those of ordinary skill in the art to predict which residues can vary without losing catalytic activity. The Office asserts that there is no art-recognized correlation between "any structure" and XI based on which those of ordinary skill in the art could predict which residues can vary from SEQ ID NO:1 without loss of catalytic activity. "Accordingly, there is no information regarding the nucleotide sequence and nucleotide composition of the corresponding encoding nucleic acids of the genus."

According to the Action, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, MPEP § 2163 requires that, when substantial variation within the genus exists, Applicants must describe a sufficient variety of species to reflect the variation within the genus. Here, the specification allegedly fails to disclose additional nucleic acids as claimed. As such the disclosure of SEQ ID NO: 2 encoding SEQ ID NO: 1 is concluded to be insufficient to represent the attributes and features common to all the members of the claimed genus.

Citing *Vas-Cath, Inc.* v. *Mahurkar,* 19 USPQ2d 1111, the Action concludes that "the specification does not 'clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'

The Action concludes that, considering the foregoing, one of ordinary skill in the art would not recognize that applicants were in possession of the claimed genus.

II. Rejections under 35 U.S.C. §112, 1st Paragraph (Lack of Enablement)

Claims 1-4, 6-20, 25, 27, and 28 were rejected for lack of enablement. The Office has admitted that the specification does enable a cultured isolated eukaryotic cell transformed with a nucleic acid construct comprising a nucleotide sequence encoding a XI comprising the amino acid sequence of SEQ ID NO: 1; and a process for producing ethanol, lactic acid, acetic acid, succinic acid, an amino acid, 1,3-propanediol, ethylene, glycerol, a ~-lactam, or cephalosporin comprising fermenting a medium containing a source of xylose with the said eukaryotic cell.

However, the specification allegedly does not enable any other embodiment as recited in the claims. The nature and breadth of the claims encompass any cultured eukaryotic host cell transformed with any nucleic acid construct comprising any nucleotide sequence encoding any XI comprising an amino acid sequence that is **at least 95% identical to SEQ ID NO: 1.**

The previously cited reference of Chica *et al.* (Curr Opin Biotechnol. 2005 16:378-84) allegedly teaches that the complexity of the structure/function relationship in enzymes has limited the general application of rational enzyme modification and design, where rational enzyme modification and design requires in depth understanding of structure/function.

The specification admittedly provides guidance, prediction, and working examples for the isolated polynucleotide *from Piromyces* sp. E2 (ATCC 76762) consisting of SEQ ID NO: 2 encoding a XI consisting of the amino acid sequence of SEQ ID NO: 1, yeast expression vectors containing said isolated polynucleotide, yeast host cells transformed with said expression vectors, and growth of said yeast host cells on xylose. However, the Office contends that the specification does not provide guidance, prediction, and working examples for making and/or using the invention as claimed.

The specification allegedly does not provide a correlation between any structure, other than the above mentioned SEQ ID NO: 2 encoding SEQ ID NO: 1, and XI activity that would enable one of ordinary skill in the art to predict which amino acids can varied from this sequence without losing the catalytic activity. There is no art-recognized correlation between "any structure" (presumably including sequence) and XI activity; no information is provided about which amino acids can vary from SEQ ID NO: 1 while still retain XI activity. The office extends this notion to the nucleotide sequences and compositions of the corresponding encoding nucleic acid.

It is posited that an enormous amount of experimentation is needed to search and screen for the claimed nucleic acid from any biological source or synthesize the nucleic acid as claimed and determine if the nucleic acid will encode a polypeptide that has XI activity. The Action notes that a general teaching regarding screening and searching for the claimed invention using assays disclosed in the specification is not considered guidance for making the claimed invention.

Therefore, in view of the overly broad scope of the claims, the specification's lack of specific guidance and prediction, the specification's lack of additional working examples, it would require undue experimentation to make and use the claimed invention.

III. Applicants' Combined Response to both § 112, First Paragraph Rejections

While Applicants disagree with the Office's analysis, they have amended the three independent claims by introducing additional structural features of a functional XI protein into claim 29 (corresponding to prior claim 12) 34 (corresponding to prior claim 16) and 39 (corresponding to prior claim 1). These features are:

(1) a first XI signature pattern;
(2) a second XI signature pattern;
(3) a catalytic triad including the following four residues at the indicated positions in SEQ ID NO:1: His 102 plus Asp 105, and Asp 340 and Lys 235; and
(4) at least one Mg-binding site that is residue Glu 233 of SEQ ID NO:1.

These structural features were well known in the art at the time of the invention to be indispensable regions XI's in general and of SEQ ID NO:1 as a preferred example of this protein. These features in the claims provide the requisite "structure-function" basis that support description and enablement as they provide the necessary basis for predictability in the scope of "functional enzymes" that have at least 95% sequence identity to SEQ ID NO:1. Examiner Nashed stated during the interview that claims including the above features and limited to "at least 95%" sequence identity (*vs.* the 70% identity that applicants were proposing at the time) were in compliance with § 112, first paragraph (a point not stated in the Interview Summary Record).

Support for this language is found in the specification at page 19, lines 27-30

> The ORF contained the amino acids shown to be important for interaction with the substrate (catalytic triad His 102, Asp 105, Asp 340 and Lys 235) and binding of magnesium (Glu 232) **(14, 26)**. Further, the two signature patterns (residues 185-194 and 230-237) developed for xylose isomerases **(20)** were present.

References 14, 26 and 20 noted in the above quote from the specification[1] are, respectively Henrick *et al.,* 1989; Vangrysperre *et al.*, 1990; and Meaden *et al.*, 1994 as listed below.

[1] As discussed in the interview, citation of these references was inadvertently omitted from the specification; however, they appear in a publication of the present inventors and their colleagues: HR. Harhangi, AS. Akhmanova, R Emmens, C van der Drift, W de Laat, JP van Dijken, M. Jetten, JT Pronk and HJM Op den Camp. Xylose metabolism in the anaerobic fungus *Piromyces* sp. strain E2 follows the bacterial pathway, *Arch Microbiol 180*:134-141 (2003). This publication corresponds to part of the present specification, and the manuscript for this paper was originally incorporated into its body. Brief examination of the language of this document immediately shows its essential identity to the disclosure in the specification (save for the omitted listing of these three numbered references). See Table 2 herein for comparison.

TABLE 2

From Specification	From Harhangi et al. 1993 Reference
The ORF contained the amino acids shown to be important for interaction with the substrate (catalytic triad His 102, Asp 105, Asp 340 and Lys 235) and binding of magnesium (Glu 232) **(14, 26).** Further, the two signature patterns (residues 185-194 and 230-237) developed for xylose isomerases **(20)** were present.	The ORF contained the amino acids shown to be important for interaction with the substrate (catalytic triad His-I02, Asp-105, Asp-340 and Lys-235) and binding of magnesium (Glu-232) **(Henrick *et al.* 1989; Vangrysperre *et al.* 1989*).** Furthermore, the two signature patterns (amino acid residues 185-194 and 230-237) developed for xylose isomerases (Fig. 1) **(Meaden *et al.* 1994)** were present. * error in document; this was a 1990 paper

The following references are therefore being submitted in support of Applicants' position.

- Bhosale *et al.* 1996[2] review paper - showing the alignment of a large number of XI's and annotation of functional regions
- Meaden *et al.*, 1994[3] - disclosing two "signature sequences" that characterize functional XI's
- Henrick *et al.*, 1987[4] – providing the first x-ray crystal analysis of XI
- Henrick *et al.*, 1989[5] – providing fuller x-ray crystal analysis of XI
- Vangrysperre *et al.*, 1990[6] - discussing conserved consensus sequence in XI's

These references define or discuss various structural features common to XI enzymes such as those now recited in the present independent claims 29, 34 and 39, and provide further illustration of what was known in the art about key regions of this class of enzymes at the time of the invention (even if some of their publication dates are later). Further support comes from two later-published documents, primarily WO04/99381 and WO06/009434 which are already of record. (*See also* page 9 of Applicants' Response dated 09-11-2007).

Applicants also believe that the Board's March 11, 2008, decision in *Ex Parte Porro* (copy attached as Exhibit 1), describes a situation fitting the present case, where the Board

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2 SH Bhosale, MB Rao, VV Deshpande, Molecular and industrial aspects of glucose isomerase, *Microbiol Rev. 60*:280-300 (1996)

3 Meaden PG, Aduse-Opoku J, Reizer J, Reizer A, Lanceman YA, Martin MF, Mitchell WJ, The xylose isomerase-encoding gene (xylA) of *Clostridium thermosaccharolyticum:* Cloning, sequencing and phylogeny of XylA enzymes, *Gene 141*:97-101 (1994)

4 K Henrick, DM Blow, HL Carrell, JP Glusker, Comparison of backbone structures of glucose isomerase from Streptomyces and Arthrobacter, *Protein Eng. 1*:467-69 (1987)

5 Henrick K, Collyer CA, Blow DM, Structures of o-xylose isomerase from *Arthrobacter* strain B3728 containing the inhibitors xylitol and D-sorbitol at 2.5 A and 2.3 A resolution, respectively. *J Mol Biol 208*:29-15 (1989)

6 Vangrysperre W, Van Damrne J, Vandekerckhove J, De Bruyne CK, Comelis R, Kersters-Hilderson H, Localization of the essential histidine and carboxylate group in xylose isomerases, *Biochem J 265*:699-705 (1990) (*note that a typographical error in the Harhangi et al. paper has the publication year as 1989)*

indicated the existence of adequate descriptive support (notwithstanding that the Board ruled against appellants in *Porro)*.

In view of the amendments of the independent claims and the remarks above, Applicants believe that the present claims all comply with the written description and enablement requirements of § 112, first paragraph, so that it would be proper to withdraw any remaining rejections under these statutory provisions.

IV. Rejection Under 35 U.S.C. 103(a) (Obviousness)

The Action maintained the rejection of Claims 1-4 and extended the rejection to new claim 25 for being obvious over the earlier cited three references:

(i) Guan *et al.* (US Pat. 5,643,758; hereinafter "Guan"); or

(ii) Karlsson *et al.* (*Eur J Biochem. 268*:6498-507, 2001; hereinafter Karlsson)

both in view of Accession No. Q9P8C9 (which presents the XI amino acid sequence from *Piromyces sp.* E2 that is 99% identical to SEQ ID NO: 1).

Guan is cited for teaching expression vectors containing promoters, prokaryotic host cells such as *E. coli* and eukaryotic host cells such as yeast, and methods for making, expressing, isolating, and purifying **any protein** fused to the *E. coli* maltose binding protein (**MBP**) using the expression vectors, the prokaryotic and the eukaryotic host cells; and that these methods and products are useful for **purifying** virtually any hybrid polypeptide molecule employing recombinant techniques (referring to the entire Guan patent).

Karlsson is cited for teaching host cells of the filamentous fungus *Trichoderma reesei* transformed with an expression vector containing a polynucleotide encoding Ce161A (EG IV).

The Office continues to contend that it would have been obvious to use yeast cells taught by Guan or *Trichoderma reesei* host cells taught by Karlsson *et al.* transformed with the polynucleotide encoding XI of Accession Q9P8C9. The skilled artisan allegedly would have been motivated transform these cells types with this sequence **in order to express and purify the XI** of Q9P8C9. Allegedly, there would and would have been a reasonable expectation of success because recombinant molecular biology techniques for heterologous or homologous expression of proteins were well developed in the art. Thus, it was within the ordinary skill in the art to make and use the claimed invention, so it is considered *prima facie* obvious.

Office's Response to Applicants' Prior Arguments and the De Bont Declaration

The Action states that Applicants' arguments filed 03/31/2008 and the De Bont Rule 132 Declaration were fully considered but not found persuasive for reasons given below.

Applicants had argued that motivation for combining the references had not been provided. In rebuttal, the Office Action listed a number of exemplary rationales that may support a conclusion of obviousness (according to MPEP § 2143):

(A) Combining prior art elements according to known methods to yield predictable results;

(B) Simple substitution of one known element for another to obtain predictable results;

(C) Use of known technique to improve similar devices (methods, or products) in the same way;

(D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The Office stated that using the products and methods taught by Guan and by Karlsson with the polynucleotide encoding the XI taught by Accession Q9P8C9 (an amino acid sequence that is 99% identical to SEQ ID NO: 1 of the instant application would yield the **predictable** result of the *recombinant expression* ***and purification***[7] of that XI. Recombinant expression **and purification** of proteins is said to provide the well recognized and well established advantage of **production of large, purified amounts** of the desired proteins.

In response to Applicants contention that there was no expectation of success, the Office countered that the instant application shows successful expression of the XI consisting of SEQ ID NO: 1 in yeast cells (*though Applicants note that this was their invention, not something provided by the prior art that the Office was using against them; see Applicants' remarks below).*

[7] Applicants are showing in boldface text the Office's repeated reference to protein purification and isolation, which is irrelevant to the present claims, just to emphasize the Office's misdirected focus in its obviousness analysis.

The Office Action states that use of yeast cells for recombinant expression and **purification** of desired proteins is well known in the art. Following the Office's somewhat ambiguous logic, then, one of ordinary skill in the art would have a reasonable expectation of success in making the claimed invention because of:

- the disclosure of the combination of cited references,
- the advanced state of the art of recombinant protein expression and purification in eukaryotic cells (such as yeast);
- the (known) means for optimizing expression **and purification** of the desired proteins in yeast; and
- the specification's disclosure of "successful expression of the XI consisting of SEQ ID NO: 1 in yeast cells,"

V. Applicants' Response to § 103 Rejection

During the discussion of this § 103 rejection in the interview, Applicants offered to provide a Rule 132 Declaration that would provide information to rebut the basis of the § 103 rejection (primarily the Office's position on expectation of success). The Examiners indicated that a showing of the unexpectedness of the Applicants' results and their discovery of a solution to a long standing problem representing a long held, but unmet, need, could overcome the *prima facie* obviousness rejection. Applicants present here the Van Dijken Declaration and the remarks below in support of the unobviousness of the rejected claims.

A long standing element in the law of obviousness is the requirement that the Office consider all objective evidence of non-obviousness in making an obviousness determination. *In re Sernaker*, 702 F.2d 289 (Fed. Cir. 1983). This includes evidence of a long-felt need and lack of success by others (*Graham v. John Deere*, 148 U.S.P.Q. 459 (1966)). The Office has not addressed these unexpected properties of the present invention and the absence of such properties in prior art beyond pointing to the desirability of these characteristics. The evidence presented herein, along with the unpredictability discussed below in the appended Declaration, clearly rebut any *prima facie* case of obviousness which might have been made.

The specification, in the paragraph bridging pages 2 and 3, emphasizes the history of unsuccessful attempt to solve the problem for which the present invention provides a solution, and citing numerous references evidencing such failures. Of particular interest are the following two documents, which are filed herewith (as part of a Supplemental IDS):

Amore *et al.*, 1989, *Appl. Microbiol, Biotechnol. 30*:351-357.

Chan *et al.* 1989 (*Appl. Microbiol, Biotechnol. 31*:524–28.

The van Dijken Declaration further cites these documents as among the stronger examples of the lack of success in expressing various heterologous XI's in yeast and the unexpectedness of the present invention.. In Section 6, Prof. Van Dijken emphasizes that the claimed sequence of XI is more closely related to XI sequences "**known not to function in yeast,** such as, *e.g.*, the *E. coli* XI, of Chan *et al.*" than it is to several thermophilic XI's that show some activity in yeast. A forceful example supporting the non-obviousness of Applicants' invention is the fact that, as described in the Amore *et al.* document, *B. subtilis* XI protein was "strongly" expressed in *S. cerevisiae* (as much as 5% of total cell protein). However, this protein lacked any XI enzymatic activity.

Prof. Van Dijken also points out that the Gardonyi *et al.*, 2003 paper[8] serves not only as an example of yet another failure to express a bacterial (*Streptomyces rubiginosus*) XI in *S. cerevisiae* – here due to misfolding, but also goes through a number of past failures and discusses various reasons, mostly hypotheses, why these XI's failed. What all these references teach is that there was no reasonable basis for the Office to conclude that there would have been any reasonable expectation of success in functionally expressing the XI as presently claimed in eukaryotic cells in general or in *S. cerevisiae* cells specifically.

In Section 5 of the Declaration, Prof. Van Dijken specifically points out how several of the Office's broad statements about why the invention is considered obvious are not reasonably applicable to the present invention. Notably, he disputes the Office's conclusion that:

> *The knowledge of persons of ordinary skill in the field of recombinant expression and purification of proteins in eukaryotic cells such as yeast and the means of optimizing this expression and purification (purportedly based on the mere combination of the 3 references) when coupled with the inventors' first showing of successful expression of XI (SEQ ID NO: 1) in yeast cells, are* ***proof that there would have been a "reasonable expectation of success" in making this invention."***

(emphasis added). The basis for his position is set out in detail in Sections 6-8. Prof. Van Dijken disputes the motivation to select the particular sequence of the present invention for use in eukaryotic cells, such as yeast, to permit them to grow on and ferment xylose to produce ethanol or other nonethanolic fermentation products. The Declaration discusses the significant distinction between the Office reliance upon the (alleged) obviousness of using recombinant techniques (in general) to increase production of a recombinant protein (in general) even if applied to a particular XI. However, as Prof. Van Dijken emphasizes, the invention concerns metabolic engineering in which a particular XI (or a close homologue thereof) is used to

[8] albeit published after Applicants' priority date – though providing "pre-filing date" history

unexpectedly produce (enzymatically active) functional XI protein *in vivo* in cells that then exploit that enzyme to ferment xylose, convert it to xylulose, which thereby enables the cells to make ethanol and other fermentation products. The unexpectedness of this success in light of the long history of failure rebuts the *prima facie* obviousness rejection. This is so even if, *arguendo*, the rejection may have been more appropriate to a claim to a method of isolating and purifying (any) XI. However, this notion is not appropriate to the present invention which imposes more stringent requirements on the expressed protein *in vivo*.

As Prof. Van Dijken has concluded (last paragraph of Sec. 8) , there is no basis for the Office's conclusion that there would have been a reasonable expectation of success "in expressing the claimed XI in active form in a eukaryotic cells, such as yeast or a fungus, under conditions that would permit the cells to metabolize xylose to xylulose and thus use xylose as their sole carbon source.

The Office Action has cited MPEP 2143 and provided a list of seven "exemplary rationales" (listed above) that may be used to support a conclusion of obviousness. The Van Dijken Declaration presents a point-by-point rebuttal of these rationales, summarized below, as applied to the present claims.

Although the present invention relies upon known methods for its genetic engineering, the results obtained were not predictable. The search for an XI that could be used to enable yeast to grow on xylose was not a simple substitution of one known element for another, and the results obtained were not predictable; rather applicants solved a long-recognized problem. Even if there no "inventive" aspect to the **techniques** used to construct the claimed transformed cells, the success of the "products" (*i.e.*, the modified cells with the long sought-after characteristics) were highly unexpected. The path to the improved product and process of the present invention was long and complex; and it was only the present inventors, not the prior art, who showed the way. Even if the results were "desired," they were not "expected." Even if those in the art knew of numerous XI genes to "try" in the quest for the present results,

> ... none of them worked, and no one knew why. Finding the right XI gene was anything but "predictable" and, as it turned out, there was no reasonable expectation that any particular XI would bring success.

Van Dijken Declaration at Section 9F.

None of the cited prior art, nor anything else known in the same or a different field, nor any "design incentive" nor any "market forces" suggested the solution that the present inventors were the first to reach. The "variations" (notably, which XI sequence would work and which would not) were not predictable to those of skill in the art; on the contrary, the art was fraught

with a history of failures, and the cited combination of references do nothing to point to a solution. Nothing tried prior to this invention provided an appropriate suggestion of what would work, despite the desire to attain the inventors' results.

On the basis of the foregoing facts and analysis, as set for the in the Van Dijken Declaration and in the Applicants remarks, it is believed that Applicants they have provided the necessary evidence to overcome any *prima facie* obviousness rejection over the cited art. It would therefore be proper to withdraw this ground for rejection.

VI. Conclusion

In view of the prior indication of possibly allowable claims, the present amendments (appearing in the form of "new" claims), the Van Dijken Declaration, and the foregoing remarks, Applicants believe that they have overcome the pending grounds for rejection under § 112, first paragraph and § 103(a). Reconsideration, withdrawal of the pending rejections and allowance of all present claims 29 – 56 are respectfully requested.

As discussed in the interview, the Examiner is respectfully requested to contact the undersigned at (202) 628-5197 if any clarification is required or if further discussion will assist in advancing this case to issue.

Respectfully submitted,

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